

Effect of tamsulosin on lower urinary tract symptoms related to double-J ureteral stent: a randomised, double-blinded, placebo controlled trial

ABSTRACT

Objective To evaluate the effect of tamsulosin on stent-related symptoms in patients undergoing double-J ureteral stenting.

Methods and materials Seventy patients (47 men and 23 women; mean age 42.5 years) who underwent double-J stent placement in adjunct to urological surgery were prospectively randomised into two groups. Group 1 included 35 patients who received 0.4 mg of tamsulosin once daily for 4 weeks; group 2 included 35 patients who received a placebo for the same protocol. All patients were interviewed by the same physician about the frequency of stent-related symptoms at 4 weeks after stent insertion.

Results Patients in group 1 showed a lower score for suprapubic pain during the filling phase and lower pain during sexual activity than group 2, although the overall pain score was not significantly different between two groups. The mean urinary urgency score was less in group 1 in comparison to the placebo group ($p=0.030$). No statistically significant differences were found between two groups concerning haematuria, urinary incontinence, frequency nor dysuria.

Conclusion Tamsulosin improves symptoms associated with double-J ureteral stents, especially body pain during sexual activity.

Keywords Urethral stent, stent-related symptoms, lower urinary tract symptoms, tamsulosin, double-J

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INTRODUCTION

Indwelling ureteral stents are a commonly used tool in urologic practices. Zimskind et al.¹ described ureteral stent placement for the first time in 1967. However, despite the documented benefits of double-J stents in preventing ureteral obstruction after urologic procedures², patients may experience stent-related symptoms and some morbidities, including urinary symptoms, stent-related body pain and sexual difficulties which, together, can severely influence the patients' quality of life and general health substantially³⁻⁸.

Authors have hypothesised several aetiologies responsible for stent-related complications such as bladder trigone irritation and renal reflux^{7,9}. Through the years, manufacturers have made innovations in stent design and materials in order to improve stent-caused problems^{10,11}, yet have failed to design an ideal stent which can significantly reduce adverse effects^{11,12}.

Given the effect of α -blockers in alleviating lower urinary tract symptoms associated with overactive bladder and benign prostate hyperplasia¹³, several studies investigated the role of these agents on stent-related symptoms using the Ureteral Stent Symptom Questionnaire (USSQ)¹³⁻¹⁷, the International Prostate Symptom Score (IPSS)¹⁷⁻²⁴, the Visual Analog Pain Score (VAPS)^{19-21,24}, or evaluation of clinical symptoms by interviewing the patients²⁵.

Tamsulosin selectively blocks α -1a/1d adrenergic receptors in smooth muscles of distal ureter, bladder trigone, bladder neck and prostate²⁶. Smooth muscle relaxation is believed to reduce bladder, neck and urethral resistance, which can improve stent-related lower urinary tract symptoms^{17,18}. The purpose of this clinical trial was therefore to evaluate the effectiveness of tamsulosin in reducing double-J stent-related symptoms in patients undergoing ureteral stenting.

METHODS AND MATERIALS

After ethics committee approval, this prospective double-blinded and placebo controlled randomised clinical trial was carried out between June 2014 and July 2015 in Sina Hospital, Tehran, Iran. The current trial was registered at www.clinicaltrials.gov as IRCT2015042221886N2.

Study population and design

Patients who underwent a double-J ureteral stenting by a single surgeon were assessed for eligibility. Stents were routinely placed before extracorporeal shock wave lithotripsy (ESWL) or following percutaneous nephrolithotomy (PCNL), ureterorenoscopy (URS), endoscopic endopyelotomy, or transureteral ureterolithotomy (TUL) for 4 weeks. Patients with at least 18 years of age and with an unilateral double-J ureteral stent were enrolled into the study after obtaining informed consent about random allocation of treatment and potential side effects of tamsulosin. The exclusion criteria included patients younger than 18 years, pregnant women, patients with bilateral stents, forgotten ureteral stent, long-standing ureteral stent placement, benign prostatic hyperplasia, previous prostatic resection, prostatitis, prostate cancer, bladder neoplasms, recent or recurrent urinary tract infection, history of chronic flank pain, patients previously treated with selective α -blockers, patients with severe cardiovascular disease, and patients affected by risk factors for erectile dysfunction.

Study procedure

Out of 110 patients who were assessed for eligibility, a total of 76 patients (47 men and 29 women, aged 20–74 years) who gave consent were enrolled in the study. Patients were randomly allocated into two groups using a computer randomisation program. In group A, the case group, 38 patients (25 men and 13 women) received a daily 0.4 mg dose of tamsulosin (Maxulosin[®], Exir Pharmaceutical Co., Borujerd, Iran). In group B, the control group, 38 patients (25 men and 13 women) received a placebo once a day for 4 weeks. The patients were given numbered containers enclosing unnamed pills. Both participants and physicians were kept blinded to the medication being prescribed.

Before the scheduled operative procedure, routine laboratory tests and imaging were performed. In all patients, an identical flexible double-J ureteral stent was used, although the length and size of stents were individualised for each patient. Stent placement was done under regional or general anaesthesia. The coiled distal end of the stent was the only part of the stent presented in the bladder. Plain abdominal X-ray film was used to assure correct stent positioning. To standardise analgesic consumption, acetaminophen 500 mg was prescribed for pain control. No procedure-related complication occurred. All study procedures were in accordance with the ethical standards of the ethics committee of Tehran University of Medical Sciences on human experimentation and with the Helsinki Declaration of 1975, as revised in 2009.

Patient assessment and outcome measurements

Four weeks after stent placement, patients were interviewed by the same physician about stent-related symptoms including suprapubic pain (filling and voiding phase), haematuria, urinary incontinence, urinary frequency, dysuria, urinary urgency, nocturia, flank pain (filling and voiding phase), genitalia pain, and flank, suprapubic or genitalia pain during sexual activity. Patients were asked to answer the questions regarding the frequency of each symptom in a five-level Likert scale – ‘never’, ‘rarely’, ‘sometimes’, ‘often’, and ‘very often’.

Statistical analysis

Statistical analysis was performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were obtained for each study variable. Chi-square, and student’s t-test were used for comparison between the two groups as appropriate; values of p less than 0.05 were considered statistically significant.

RESULTS

Out of 76 enrolled patients, 70 (92.1%) completed the study. Therapies were well tolerated and no patients had to terminate medication owing to adverse effects, and none underwent stent removal prior to the due date. Characteristics of the study population are presented in Table 1. Group A (35 patients) consisted of 22 men and 13 women (mean age 43.0 ± 12.2 years), and group B consisted of 25 men and 10 women (mean age 42.0 ± 12.4 years). A total of 45 patients (64.2%) underwent transurethral lithotripsy, nine patients (12.8%) underwent percutaneous nephrolithotripsy or ESWL, while endopyelotomy for ureteropelvic junction stricture was performed in 16 patients (22.8%). No statistically significant differences were found regarding gender, age, weight, height, nor indication of stent placement between the case and control groups.

Scores 0 to 4 were attributed respectively to the frequency of scale of symptoms stated by patients, with 0 representing ‘never’ and 4 representing ‘very often’. Table 2 summarises the overall results of our study. Student’s t-test was used to examine the differences of means between groups. As shown in the table, patients receiving tamsulosin expressed higher scores (1.51 ± 1.66) for nocturia than patients in the control group (0.80 ± 1.07) ($p=0.037$). The mean score for pain in

Table 1. Patient characteristics in the two groups.

	Group A: Tamsulosin	Group B: Placebo	p value
No. of patients	35	35	NA
Male:Female	22:13	25:10	0.58 [Chi-square]
Age (years) ± SD	43.0 ± 12.2	42.0 ± 12.4	0.72 [Student's t test]
Weight (kg) ± SD	71.6 ± 15.1	70.6 ± 15.3	0.78 [Student's t test]
Height (cm) ± SD	167.5 ± 8.1	166.6 ± 9.7	0.66 [Student's t test]
Indication of stent placement			
TUL	20	25	0.18 [Chi-square]
PCNL/ESWL	7	2	
Endoscopic endopyelotomy	8	8	

the flank, suprapubic and genital areas during sexual activity was lower in patients receiving tamsulosin in comparison to patients receiving the placebo (p values=0.047, 0.041 and 0.047, respectively). Patients treated with tamsulosin showed lower suprapubic pain in filling phase scores (0.49 ± 0.70) than the control group (0.94 ± 1.11) (p=0.043). The mean urinary urgency score was 0.6 in group 1 and 1.1 in the placebo group (p=0.030). No statistically significant differences were found between the two groups concerning haematuria, urinary incontinence, frequency, dysuria, nor overall pain score (p values >0.05).

DISCUSSION

The results of this double-blind, randomised, placebo-controlled study showed that tamsulosin is effective in relieving stent-related symptoms specially in alleviating pain during sexual activity.

Current indications for ureteral stents in urgent conditions include unbearable acute renal colic, obstructive pyelonephritis and renal failure secondary to ureteral obstruction³. Endoscopic procedures can be followed by stent placement as a safety measure²⁷ in several situations, including ureteral oedema, ureteral perforation, solitary kidney, transplant kidney and history of renal failure. There are also relative indications for indwelling ureteral stents such as passive dilation of ureteral orifice and ureter, before ESWL in stones larger than 2 cm, long-lasting impacted stone, endoscopic procedures lasting over 45 minutes, and pregnancy^{2,7}.

However, despite widespread use of indwelling ureteral stents, there is considerable controversy over the necessity of stent placement after uncomplicated ureteroscopic lithotripsy²⁸. Even after choosing the correct stent size and proper placement, indwelling ureteral stents are associated with inevitable morbidities in over 80% of patients²⁹, including

urinary symptoms, haematuria, pain and sexual difficulties which all lead to reduced health-related quality of life⁶. Some researchers report that the position and completeness of the stent's lower loop and proper attention to detail throughout stent placement have an effect on symptom severity^{30,31}. For example, an ureteral stent was better tolerated after periureteral injection of botulinum toxin type A after stent placement by significantly decreasing pain and narcotic requirement³².

However, the exact pathophysiology of stent-related symptoms is not fully understood. It is assumed that lower ureteral smooth muscle spasms, involuntary bladder contraction triggered by neuronal-rich trigone irritation, and urine reflux to the kidneys due to increased bladder outlet resistance are responsible factors^{11,14,15,21,33}. α -blockers are recommended as expulsive therapy for ureteral stones and to decrease recurrent colic episodes. They are believed to relieve stent-related morbidity by different ways³⁴⁻³⁶. Blocking α -adrenergic receptors reduces muscle tone of prostatic urethra, bladder trigone and ureter which leads to decreased bladder outlet resistance, voiding pressure, and urinary reflux¹⁷. However, the effectiveness of these medications and proper therapeutic protocols for alleviation of stent-related symptoms are yet to be discovered by further investigations. Results of the current study showed that tamsulosin (a selective α_{1A} antagonist) can control several stent-related morbidities.

The effectiveness of α -blockers in relieving stent-related symptoms has been investigated by several studies, including patients receiving either alfuzosin 10 mg^{13,14,16,25,37}, tamsulosin 0.4 mg^{15,17,22,23,17}, tamsulosin 0.2 mg^{19,20}, terazosin 4 mg^{21,38}, terazosin 2 mg²¹, or a placebo for 1–6 weeks' treatment. Damiano et al.¹⁵ released the first report of the benefits of a daily dose of tamsulosin 0.4 mg in a prospective study comparing tamsulosin to placebo in 75 patients using the USSQ. Although this study was not double-blinded nor

Table 2. Comparison of symptom frequency scores in the two groups.

	Group A: Tamsulosin	Group B: Placebo	Difference (p value)
Suprapubic pain (filling phase)	0.49 ± 0.70	0.94 ± 1.11	0.043
Suprapubic pain (voiding phase)	0.57 ± 0.69	0.94 ± 1.30	0.142
Flank pain (filling phase)	0.97 ± 1.27	1.29 ± 1.31	0.314
Flank pain (voiding phase)	0.83 ± 1.12	0.94 ± 1.25	0.690
Genital pain	0.91 ± 1.29	0.83 ± 1.17	0.772
Flank pain during sexual activity	0.03 ± 0.16	0.17 ± 0.38	0.047
Suprapubic pain during sexual activity	0.06 ± 0.23	0.23 ± 0.42	0.041
Genitalia pain during sexual activity	0.03 ± 0.16	0.20 ± 0.47	0.047
Overall pain score	0.48 ± 0.45	0.69 ± 0.68	0.140
Haematuria	1.20 ± 1.13	1.77 ± 1.16	0.041
Urinary incontinence	0.37 ± 0.87	0.31 ± 0.53	0.743
Urinary frequency	2.60 ± 1.55	2.49 ± 1.46	0.753
Dysuria	1.63 ± 1.43	1.74 ± 1.44	0.741
Urinary urgency	0.60 ± 1.73	1.17 ± 1.33	0.030
Nocturia	1.51 ± 1.66	0.80 ± 1.07	0.037

placebo-controlled, the authors found that patients receiving tamsulosin had their general health better preserved. In another study performed by Wang et al.¹⁷ on 154 patients using the same measurement tool, those receiving tamsulosin showed lower stent-related symptoms and better quality of life than patients receiving a placebo.

Using both IPSS and VAPS, the effect of lower dose of tamsulosin (0.2 mg once a day) alone and in combination with tolterodine or solifenacin on stent-related symptoms was investigated by Lee et al.¹⁹ and Lim et al.²⁰, respectively. Lee et al. found that only the storage symptom scores were significantly lower in patients receiving either mono- or combination therapy than patients treated with no medication. The author stated that correct placement of the stent is therefore more important than medication in reducing stent-related storage symptoms¹⁹. Conversely, Lim showed that combination therapy with tamsulosin and solifenacin can better improve both irritative and obstructive symptoms than tamsulosin alone or compared to receiving no medication²⁰; the results were later confirmed by Shalaby et al.²³. Further, improvement of stent-related symptoms by α -blockers was found to be independent to the type of α -blocker, as showed by Dellis et al.³⁷ comparing tamsulosin and alfuzosin. To the best of our knowledge, there is only one study¹⁸ on α -blocker (doxazosin) ineffectiveness in reducing stent-related symptoms.

In a recent meta-analysis performed by Lamb et al.³⁵ including 461 patients from five studies, all studies showed a reduction

in the USSQ urinary symptom score and body pain scores in patients receiving either tamsulosin or alfuzosin. However, general health and sexual matters improvement were not statistically significant. Results of a further 12 studies including a total number of 946 patients' data were meta-analysed by Yakoubi et al.³⁶. Analyses showed a significant reduction in urinary symptoms and pain scores as well as general health improvement in patients receiving α -blockers.

In our study, the reduction in pain scores in patients treated with tamsulosin was more evident when compared to during sexual activity in all three areas – flank, genital and suprapubic. Ureteral stents were showed to impair the quality of sexual life in both men and women⁸. Erectile dysfunction was indicated as the main source of sexual distress in men, probably related to lower urinary tract symptoms and stent permanence. In women, sexuality can be severely impaired as a result of stent-related psychological distresses⁸.

We also found tamsulosin effective in reducing haematuria and urinary urgency, although, patients treated with tamsulosin had increased rate of nocturia than patients receiving placebo. Nocturia has not reported as an adverse effect of tamsulosin previously, so this finding should be investigated by larger-scale studies. Koseoglu et al.³⁹ found tamsulosin ineffective in reducing nocturia in patients being treated for benign prostatic hyperplasia. In another study, combination of α -blockers with zolpidem was shown to better reduce nocturia than α -blockers alone⁴⁰.

Our study had several limitations. First, our sample size was statistically small in order to detect small differences between two groups. Second, some patients did not complete the study. Third, we utilised clinical interviews with the patients to evaluate urinary symptoms, whereas Joshi et al.⁶ has developed a specific tool for assessing stent-related symptoms called the USSQ. Fourth, the quantity of the analgesics used by patients was not reliably reported. Finally, we did not investigate any adverse effects made by α -blocker use, although therapies were well tolerated and no patients had to discontinue medication owing to side effects. Therefore, further large-scale, randomised, prospective studies are needed to obtain more accurate information.

CONCLUSION

The use of tamsulosin 0.4 mg once daily in patients with unilateral ureteral stenting significantly improved stent-related urinary symptoms, especially the body pain during sexual activity. Therefore, tamsulosin should be considered for patients who complain of stent-related symptoms. In the future, large-scale, prospective and randomised studies will be needed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was undertaken before surgery based on the ethical code of the Tehran University of Medical Sciences Ethics Committee. This trial was registered at www.clinicaltrials.gov as IRCT2015042221886N2. The information is published without the name of the patients. Information, data and photos can be provided if requested.

COMPETING INTERESTS

All authors claim that there is not any potential competing or conflict of interest.

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